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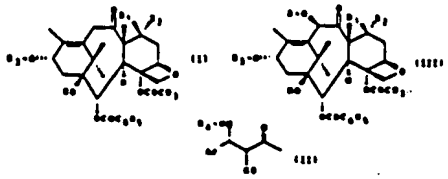
(54) Title: PROCESS FOR THE PREPARATION OF TAXANE DERIVATIVES, NOVEL TAXANES SO OBTAINED AND ANTITUMOUR AND ANTILEUKAEMIA COMPOSITIONS CONTAINING SAME

(54) Titre: PROCEDE DE PREPARATION DE DERIVES DU TAXANE, NOUVEAUX TAXANES AINSI OBTENUS ET LES COMPOSITIONS ANTITUMORALES ET ANTILEUCEMIQUES QUI LES CONTIENNENT

(57) Abstract



Process for the electrochemical preparation of taxane derivatives of general formula (I), based on a taxane derivative of general formula (III). The invention also concerns pharmaceutical compositions with outstanding antitumour and antileukaemia properties which contain a novel product of general formula (I) wherein R_3 is a radical of general formula (II). In general formulae (I) and (III), R is a hydrogen atom or an acetyl or alkoxyacetyl radical, one of the symbols R_1 or R_2 is a hydrogen atom and the other is a hydroxy radical, R_3 is a hydrogen atom or a radical of general formula (II) wherein Ar is an aryl radical and R_4 is a benzoyl radical or a R_5-O-CO- radical in which R_5 is an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclyl radical.

(57) Abrégé

Procédé de préparation de dérivés du taxane de formule générale (I), par voie électrochimique, à partir d'un dérivé du taxane de formule générale (III) et les compositions pharmaceutiques qui contiennent un nouveau produit de formule générale (I) dans laquelle R_3 représente un radical de formule générale (II) qui présentent des propriétés antitumorales et antileucémiques remarquables. Dans les formules générales (I) et (III), R représente un atome d'hydrogène ou un radical acétyle ou alcoxyacétyle, un des symboles R_1 ou R_2 représente un atome d'hydrogène et l'autre représente un radical hydroxy, R_3 représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle: Ar représente un radical aryle et R_4 représente un radical benzoyle ou un radical R_5-O-CO- dans lequel R_5 représente un radical alcoyle, alcényle, cycloalcoyle, cycloalcényle, bicycloalcoyle, phényle ou hétérocyclyle.

VERIFIED TRANSLATION OF PCT 54257/94

IN THE MATTER OF an Australian
Application corresponding to
PCT Application PCT/FR93/01102

I, Philip Arnold KENDALL BSc ARCS MS PhD,
c/o Europa House, Marsham Way, Gerrards Cross, Buckinghamshire,
England, do solemnly and sincerely declare that I am conversant with the English and French languages and am a competent translator thereof, and that to the best of my knowledge and belief the following is a true and correct translation of the PCT Application filed under No. PCT/FR93/01102.

Date: 25 April 1995

P A Kendall

P. A. KENDALL
For and on behalf of RWS Translations Ltd.

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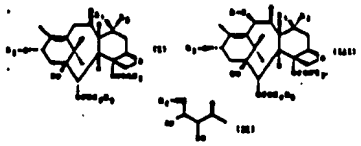

Process for the electrochemical preparation of taxane derivatives of general formula (I), based on a taxane derivative of general formula (III). The invention also concerns pharmaceutical compositions with outstanding antitumour and antileukaemia properties which contain a novel product of general formula (I) wherein R_3 is a radical of general formula (II). In general formulae (I) and (III), R is a hydrogen atom or an acetyl or alkoxyacetyl radical, one of the symbols R_1 or R_2 is a hydrogen atom and the other is a hydroxy radical, R_3 is a hydrogen atom or a radical of general formula (II) wherein Ar is an aryl radical and R_4 is a benzoyl radical or a R_5-O-CO- radical in which R_5 is an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclyl radical.

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Procédé de préparation de dérivés de taxane de formule générale (I), par voie électrochimique, à partir d'un dérivé du taxane de formule générale (III) et les compositions pharmaceutiques qui contiennent un nouveau produit de formule générale (I) dans laquelle R_3 représente un radical de formule générale (II) qui présentent des propriétés antitumorales et antileucémiques remarquables. Dans les formules générales (I) et (III), R représente un atome d'hydrogène ou un radical acétyle ou alcoxyacétyle, un des symboles R_1 ou R_2 représente un atome d'hydrogène et l'autre représente un radical hydroxy, R_3 représente un atome d'hydrogène ou un radical de formule générale (II) dans laquelle: Ar représente un radical aryle et R_4 représente un radical benzoyle ou un radical R_5-O-CO- dans lequel R_5 représente un radical alcoyle, alcényle, cycloalcoyle, cycloalcényle, bicycloalcoyle, phényle ou hétérocyclyle.

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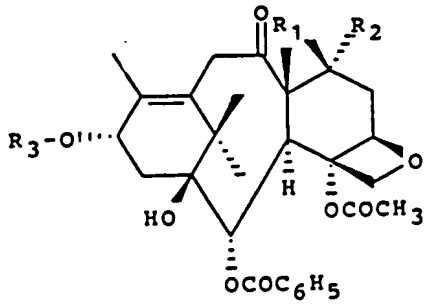
Process for the preparation of taxane derivatives, new taxanes thereby obtained and antitumour and antileukaemic compositions containing them

The present invention relates to a new process for the preparation of taxane derivatives of general formula:

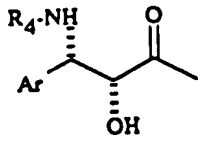


(I)

in which:

one of the symbols R_1 and R_2 represents a hydrogen atom and the other represents a hydroxyl radical,

- R_3 represents a hydrogen atom or a radical of general formula:



(II)

in which

Ar represents an aryl radical, and

R_4 represents a benzoyl radical or a radical R_5-O-CO in which R_5 represents an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclic radical.

More especially, the present invention relates to a process for the preparation of the products of general formula (I) in which, R_1 and R_2 being defined as above, R_3 represents a hydrogen atom or a radical of general formula (II) in which:

Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from fluorine or chlorine atoms and alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals containing 1 to 4 carbon atoms and the aryl radicals are phenyl or α- or β-naphthyl radicals, or a 5-membered aromatic heterocyclic radical containing one or more identical or different atoms chosen from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents chosen from halogen (fluorine, chlorine) atoms and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion

contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano, carboxyl and carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms, and

R_4 represents a benzoyl radical or a radical R_5-O-CO- in which R_5 represents:

- an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from fluorine or chlorine atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino, morpholino and 1-piperazinyl (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or

with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms) radicals, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl, cyano and carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,

- a phenyl radical optionally substituted with one or more radicals chosen from alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms

- or a saturated 4- to 6-membered nitrogenous heterocyclic radical optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

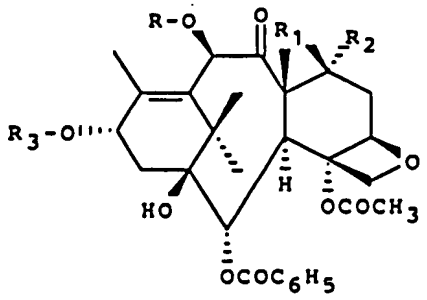
on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, and

Still more especially, the present invention relates to the preparation of the products of general formula (I) in which, R_1 and R_2 being defined as above, R_3 represents a radical of general formula (II) in which Ar represents a phenyl radical optionally substituted with a fluorine or chlorine atom or with an

alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino, alkoxycarbonylamino or trifluoromethyl radical or a 2- or 3-thienyl or 2- or 3-furyl radical, and R_4 represents a benzoyl radical or a radical R_5-O-CO- for which R_5 represents a t-butyl radical.

The products of general formula (I) in which R_1 and R_2 are defined as above, and R_3 represents a radical of general formula (II) in which Ar represents a heterocyclic radical defined as above and R_4 represents a benzoyl radical or a radical of general formula R_5-O-CO in which R_5 is defined as above, constitute new products which possess noteworthy antitumour and antileukaemic properties.

According to the present invention, the products of general formula (I) may be obtained by electrolytic reduction of a product of general formula:

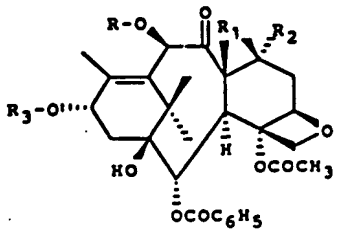


(III)

in which R represents a hydrogen atom or an acetyl or alkoxyacetyl radical and R_1, R_2 and R_3 are defined as above.

According to the invention, the reduction of

the group R-O- is effected electrochemically according to the following reaction:



$$\xrightarrow{+\,2e^- + 2H^+} \quad (I)$$

(I ; R_1 = OH and R_2 = H ; R_1 = H and R_2 = OH)

The electrolytic reduction, starting from a product of general formula (III), is carried out in an electrolyser containing a catholyte consisting of a carrier electrolyte containing magnesium, calcium, cerium^{III}, strontium or lithium ions or, where appropriate, when R represents an acetyl or alkoxyacetyl radical, ammonium (NH_4^+) ions and of a solvent or mixture of solvents or aqueous-organic mixture in which the product of general formula (III) is dissolved at a concentration between 0.1 g/l and saturation of the solution.

The theoretical quantity of electricity needed for effecting the reduction of a product of general formula (III) to a product of general formula (I; R_1 = OH and R_2 = H) and (I; R_1 = H and R_2 = OH) is 2 faradays (or 193,000 coulombs) per molecule.

Depending on the conditions of carrying out the electrolytic process, it is possible to obtain preferentially the product of general formula (I) for which R_1 represents a hydroxyl radical and R_2 represents

a hydrogen atom, depending on the nature of the electrolyte and the acidity of the medium. Generally, epimerization is not seen when the electrolytic reduction is performed in the presence of ammonium ions, the anode compartment containing a protonic acid.

Preferably, the reduction is performed in a diaphragm electrolyser.

According to an embodiment of the process according to the invention, the electrolytic reduction is performed in an electrolyser containing a cathode, a cathode compartment, a separating diaphragm, an anode compartment and an anode, the characteristics of which are as follows:

a) the cathode consists of an electrically conducting material on which reduction takes place at a potential above that of the reduction of the solvent or of one of the constituents of the carrier electrolyte, or at a potential such that the reduction of the solvent or of one of the constituents of the carrier electrolyte is not sufficiently extensive to interfere with the reduction of the product,

b) the cathode compartment contains the catholyte which consists of a solution of the product of general formula (III) in an organic or aqueous-organic medium and of an electrolyte containing magnesium, calcium, cerium^{III}, strontium or lithium ions or, where appropriate, ammonium (NH_4^+) ions. When the process is carried out in the presence of ammonium ions, the pH

may be maintained at a slightly alkaline value, that is to say preferably between 7 and 9, by adding ammonia solution,

c) the separating diaphragm consists of a porous material such as a plate, a sleeve or a candle of sintered glass or porcelain, or of an ion exchange membrane, preferably a cation exchange membrane,

d) the anode compartment contains either the anolyte, preferably consisting of the same solvent or mixture of solvents and the same carrier electrolyte as that used in the cathode compartment, or else a dilute acid in the same solvent or mixture of solvents as that contained in the catholyte,

e) the anode consists of an electrically conducting material whose nature is not critical for carrying out the process.

Generally, the anode consists of an electrically conducting material which cannot be attacked under the conditions of the electrolysis, such as, for example, polished platinum, solid or on a conducting support, graphite or vitreous carbon.

Preferably, the cathode consists of a layer of mercury.

The carrier electrolyte consists of a magnesium or calcium or, where appropriate, ammonium salt, such as magnesium chloride, calcium chloride, cerium^{III} chloride, strontium chloride, lithium chloride or ammonium chloride, which is soluble in the solvent

or mixture of solvents. Generally, protic solvents which readily solubilize the products of general formula (I) and (III), and which enable the products of general formula (I; R_1 = OH and R_2 = H) and (I; R_1 = H and R_2 = OH) to be readily isolated, are used. Preferably, the solvents will be chosen from aliphatic alcohols containing 1 to 4 carbon atoms, such as methanol, ethanol, isopropanol or t-butanol, and the aqueous-organic mixture is an alcohol/water mixture.

The pH must be compatible with the stability of the substrate, and it may be maintained at a slightly alkaline value during the electrolysis, that is to say preferably between 7 and 9, by adding aqueous ammonia solution or by bubbling in ammonia gas when ammonium chloride is used.

The nature of the diaphragm separating the anolyte from the catholyte is not an essential feature of the invention. Thus, it is possible to use any diaphragm of known type, consisting of a porous material such as sintered glass or porcelain with or without a conducting gel limiting diffusion of the reactants, or of ion exchange membranes, preferably cation exchange membranes. When the anolyte contains a dilute acid, it is especially advantageous to use a cation exchange membrane in order to maintain the pH in the catholyte by migration of H^+ ions through the membrane during the electrolysis. The membranes can be of the homogeneous or heterogeneous type, and they can

optionally be reinforced with a screen. Preferably, membranes which do not swell, which do not crinkle and which are stable in the presence of the various constituents of the anolyte and the catholyte are used.

According to a preferred embodiment of the invention, the anode, the cathode and the separating diaphragm are arranged according to horizontal parallel planes in the case of a cathode consisting of a layer of mercury.

The temperature of the electrolysis bath is generally between 0 and 30°C.

The electrolysis is performed at a controlled potential; the latter may be set at between -1.65 and -2.1 volts approximately relative to a calomel reference electrode, depending on the nature of the cation of the electrolyte.

The theoretical quantity of electricity employed is 2 faradays (or 193,000 coulombs) per mole of a product of general formula (III). In practice, the quantity of electricity used can be from 2 to 5 times the theoretical quantity, but can also be very considerably higher.

Preferably, the reaction is monitored by the disappearance of the starting material, this disappearance being determined by thin-layer chromatography.

The catholyte may be circulated, for example through the action of a pump. The circuit can, in

addition, comprise ancillary devices such as heat exchangers or expansion tanks; such an expansion tank makes it possible, in particular, to feed the catholyte with the product of general formula (III) and also enables fluid to be drawn off for extraction of the products of general formula (I).

The anolyte may also undergo circulation. According to a preferred embodiment of the invention, the catholyte circuit is similar to that of the anolyte, thereby enabling the pressures on each side of the separating diaphragm to be balanced.

According to another particular embodiment of the invention, inserts are arranged in the anode and cathode compartments. These inserts serve to avoid, on the one hand distortions of the ion exchange membrane, and on the other hand contacts between this membrane and the electrodes. They also serve to improve the concentration homogeneity of the catholyte.

In the absence of an insert, the speed of circulation of the catholyte in the cathode compartment is usually greater than 10 cm/s, and preferably greater than 50 cm/s. When an insert is used, the apparent speed of the catholyte (speed in the cathode compartment assumed to be without an insert) is usually greater than 1 cm/s, and preferably greater than 10 cm/s.

According to another embodiment of the invention, the cell can consist simply of a

parallelepipedal or cylindrical vessel made of a material which is inert with respect to the constituents of the electrolytes.

Generally speaking, any electrolytic cell containing an anode and a cathode separated by one or more diaphragms providing for ionic conductivity is capable of being employed, the arrangement of the components not being critical for carrying out the process.

The products of general formula (I) obtained by carrying out the process according to the invention are separated by application of the usual methods.

Since carrying out the process according to the invention yields, where appropriate starting from a particular product of general formula (III), a mixture of the corresponding products of general formula (I) for which, on the one hand R_1 represents a hydroxyl radical and R_2 represents a hydrogen atom, and on the other hand R_1 represents a hydrogen atom and R_2 represents a hydroxyl radical, the separation of the products thereby obtained may be performed according to known methods such as chromatography.

The products of general formula (III) in which R represents a hydrogen atom or an acetyl radical and R_3 represents a hydrogen atom correspond, respectively, to 10-deacetylbaccatin III and to baccatin III, which may be isolated according to known methods from the extracts of different varieties of yew

(Taxus sp.).

The products of general formula (III) in which R represents a hydrogen atom or an acetyl radical and R_3 represents a radical of general formula (II) in which Ar represents an aryl radical and R_4 represents a benzoyl radical correspond, respectively, to 10-deacetyltaxol and to taxol, which may be obtained according to the processes described in European Patents EP 0,253,739, EP 0,336,840, EP 0,400,971 and EP 0,428,376 or in International Application PCT WO 92/09,589.

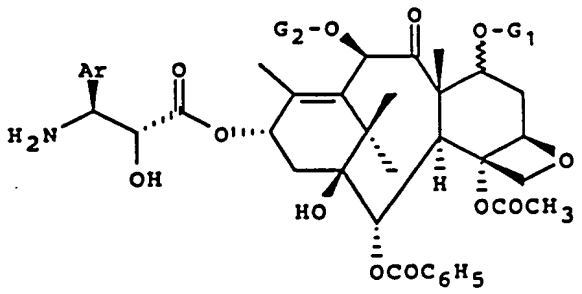
The products of general formula (III) in which R represents a hydrogen atom or an acetyl radical and R_3 represents a radical of general formula (II) in which Ar represents an aryl radial and R_4 represents a t-butoxycarbonyl radical may be obtained according to the processes described in European Patents EP 0,253,738 and EP 0,336,841 or in International Application PCT WO 92/09,589.

The products of general formula (III) in which R represents a hydrogen atom or an acetyl or alkoxyacetyl radical and R_3 represents a radical of general formula (II) in which R_4 represents a benzoyl radical or a radical R_5-O-CO- may be obtained by the action of benzoyl chloride or of a reactive derivative of general formula:

$$R_5\text{-O-CO-X} \quad \text{(IV)}$$

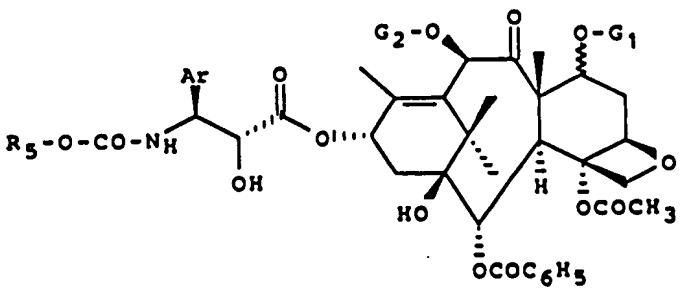
in which X represents a halogen (fluorine, chlorine)

atom or a residue -O-R_5 or -O-CO-R_5, on a baccatin III or 10-deacetylbaccatin III derivative of general formula:



(V)

in which Ar is defined as above, G_1 represents a group protecting the hydroxyl function, such as a trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl or triarylsilyl radical, in which each alkyl portion contains 1 to 4 carbon atoms and each aryl portion preferably represents a phenyl radical, and G_2 represents a hydrogen atom or an acetyl or alkoxyacetyl (methoxyacetyl) radical, to give a product of general formula:



(VI)

in which Ar, R_5, G_1 and G_2 are defined as above,

followed by replacement of the protective group G_1 and, where appropriate, of the radical G_2 by hydrogen atoms.

Generally, the action of the reagent of general formula (IV) on the baccatin III or 10-deacetylbaccatin III derivative of general formula (V) is performed in an organic solvent such as an ester, for instance ethyl acetate, in the presence of an inorganic or organic base such as sodium bicarbonate, at a temperature of between 0 and 50°C, and preferably in the region of 20°C.

Generally, the replacement of the protective group G_1 and of the radical G_2 of the product of general formula (VI) by a hydrogen atom is effected by treatment in an acid medium such as, for example, hydrochloric acid dissolved in an aliphatic alcohol containing 1 to 3 carbon atoms (methanol, ethanol, isopropanol) or aqueous hydrofluoric acid at a temperature of between 0 and 40°C when G_1 represents a silyl radical and G_2 represents an alkoxyacetyl radical.

The new products of general formula (I) in which R_1 and R_2 are defined as above and R_3 represents a radical of general formula (II) in which Ar is represents a heterocyclic radical defined as above and R_4 represents a benzoyl radical or a radical of general formula R_5-O-CO in which R_5 is defined as above manifest significant inhibitory activity with respect to abnormal cell proliferation, and possess therapeutic

properties permitting the treatment of patients having pathological conditions associated with abnormal cell proliferation. The pathological conditions include the abnormal cell proliferation of malignant or non-malignant cells of various tissues and/or organs, comprising, without implied limitation, muscle, bone or connective tissue, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive system, pancreas and thyroid or adrenal glands. These pathological conditions can also include psoriasis, solid tumours, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanoma, multiple myeloma, chronic lymphocytic leukaemia and acute or chronic granulocytic lymphoma. The new products according to the invention are especially useful for the treatment of cancer of the ovary. The products according to the invention may be used to prevent or delay the appearance or reappearance of the pathological conditions, or to treat these pathological conditions.

The products according to the invention may be administered to a patient according to different dosage forms suited to the chosen administration route, which is preferably the parenteral route. Parenteral administration comprises intravenous, intraperitoneal, intramuscular or subcutaneous administration.

Intraperitoneal or intravenous administration is more especially preferred.

The present invention also comprises pharmaceutical compositions containing at least one product of general formula (I), in a sufficient amount suitable for use in human or veterinary therapy. The compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants, vehicles or excipients. Suitable vehicles include diluents, sterile aqueous media and various non-toxic solvents. Preferably, the compositions take the form of aqueous solutions or suspensions, of injectable solutions which can contain emulsifying agents, colourings, preservatives or stabilizers.

The choice of adjuvants or excipients may be determined by the solubility and the chemical properties of the product, the particular mode of administration and good pharmaceutical practice.

For parenteral administration, sterile, aqueous or non-aqueous solutions or suspensions are used. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petrolatum or injectable organic esters such as ethyl oleate may be used. The sterile aqueous solutions can consist of a solution of a pharmaceutically acceptable salt dissolved in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately

adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

It is clearly understood that all the products participating in the compositions according to the invention must be pure and non-toxic in the amounts used.

The compositions can contain at least 0.01 % of therapeutically active product. The amount of active product in a composition is such that a suitable dosage can be prescribed. Preferably, the compositions are prepared in such a way that a single dose contains from 0.01 to 1000 mg approximately of active product for parenteral administration.

The therapeutic treatment may be performed concurrently with other therapeutic treatments including antineoplastic drugs, monoclonal antibodies, immunotherapy or radiotherapy or biological response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (a, b or d) and TNF. Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents, for instance nitrogen mustards such as mechloretamine, cyclophosphamide, melphalan and

chlorambucil, alkyl sulphonates such as busulfan, nitrosoureas such as carmustine, lomusine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products, for instance vinca alkaloids such as vinblastine, vincristine and vendesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for instance cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocortical suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethinyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

The doses used for carrying out the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the

administration form, the particular product selected and features distinctive to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders due to abnormal cell proliferation. The products according to the invention may be administered as often as necessary to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require low or zero maintenance doses. Generally, low doses will be used at the beginning of the treatment and, if necessary, increasingly stronger doses will be administered until an optimum effect is obtained. For other patients, it may be necessary to administer maintenance doses 1 to 8 times a day, and preferably 1 to 4 times, according to the physiological requirements of the patient in question. It is also possible that some patients may require the use of only one to two daily administrations.

In man, the doses are generally between 0.01 and 200 mg/kg. For intraperitoneal administration, the doses will generally be between 0.1 and 100 mg/kg, preferably between 0.5 and 50 mg/kg and still more specifically between 1 and 10 mg/kg. For intravenous administration, the doses are generally between 0.1 and 50 mg/kg, preferably between 0.1 and 5 mg/kg and still more specifically between 1 and 2 mg/kg. It is understood that, in order to choose the most suitable

dosage, account should be taken of the administration route, the patient's weight, general state of health and age and all factors which may influence the efficacy of the treatment.

The examples which follow illustrate the present invention.

EXAMPLE 1

The electrolytic reduction of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (or docetaxel or Taxotere®) is carried out in an electrolysis cell possessing the following characteristics:

- the cell is a 100-cm^3 glass vessel divided into two compartments by a cation exchange membrane,
- the cathode is a layer of mercury whose useful surface area is approximately 10 cm^2,
- the anode is a platinum grid,
- the reference electrode is a saturated calomel electrode.

4 cm^3 of a solution containing the following are introduced into the cathode compartment:

- 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate . . . . . 51.1 mg
- calcium chloride . . . . . q.s. 0.05M
- methanol . . . . . q.s. 10 cm^3

10 cm^3 of the same mixture not containing the substrate are introduced into the anode compartment.

After de-aeration of the solution for 10 minutes by bubbling a stream of argon through it, this stream being maintained throughout the period of the electrolysis, the cathode potential is set at -1.95 volts relative to the reference electrode.

The solution is electrolyzed for the time needed for the passage of 14.2 coulombs.

20 μl of acetic acid are added to the electrolysate. After the solvent has been removed under reduced pressure at a temperature below 35°C, the residue is taken up with 10 cm^3 of ethyl acetate and 10 cm^3 of water. The product is extracted with 10 cm^3 and twice 5 cm^3 of ethyl acetate. After the organic phase, separated after settling has taken place, has been dried over magnesium sulphate, the solvent is evaporated off under reduced pressure at a temperature below 35°C. 42.3 mg of crude product are thereby obtained, the constituents of which are separated by preparative thin-layer chromatography on silica gel (thickness: 0.25 mm), eluting with a dichloromethane/methanol/acetonitrile (84:8:8 by volume) mixture. 7.4 mg of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate, that is to say a product of general formula (I) for which R_1 represents a hydroxyl

radical and R_2 represents a hydrogen atom, are thereby obtained in a 15 % yield, and 9.6 mg of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate, that is to say a product of general formula (I) for which R_1 represents a hydrogen atom and R_2 represents a hydroxyl radical, are thereby obtained in a 20 % yield.

EXAMPLE 2

The electrolytic reduction of 2α-benzoyloxy-4,10β-diacetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-benzoylamino-3-phenyl-2-hydroxypropionate (or taxol) is performed in an electrolysis cell possessing the following characteristics:

- the cell is a 10-cm^3 glass vessel divided into 2 compartments by a cation exchange membrane,
- the cathode is a layer of mercury whose useful surface area is 4 cm^2,
- the anode is a platinum grid,
- the reference electrode is a saturated calomel electrode.

10 cm^3 of a solution containing the following are introduced into the cathode compartment:

- 2α-benzoyloxy-4,10β-diacetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-1-taxen-13α-yl (2R,3S)-3-benzoylamino-3-phenyl-2-hydroxypropionate . . . . . 61.9 mg
- ammonium chloride . . . . . q.s. 0.1M

- ammonia solution [33 % (w/v) aqueous solution . . . . . 0.2 cm^3
- methanol . . . . . q.s. 10 cm^3

10 cm^3 of a 0.1M solution of ammonium chloride in methanol are introduced into the anode compartment.

The solution is de-aerated by bubbling argon through it for 10 minutes, and the cathode potential is then set at -1.8 volts relative to the reference electrode until 14 coulombs have passed. The potential is then set at -1.85 volts. After the passage of 42 coulombs in total, the electrolysis is stopped. 0.1 cm^3 of pure acetic acid is added and the solvent is then removed by concentration under reduced pressure at a temperature below 35°C. The residue obtained is taken up with 10 cm^3 of water, and the product is then extracted with 10 cm^3 and then twice 5 cm^3 of ethyl acetate. The organic phase is washed with 10 cm^3 of 0.2M aqueous phosphate buffer solution, pH 7.4. After drying and concentration to dryness of the organic phase, 49.7 mg of a crude product are obtained, which product is purified by preparative thin-layer chromatography on silica gel (thickness: 0.25 mm), eluting with an ethyl acetate/dichloromethane/methanol (55:40:5 by volume) mixture. 26.3 mg of 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-benzoylamiuo-3-phenyl-2-hydroxypropionate are thereby isolated in a 45 %

yield, which product possesses the following characteristics:

- proton nuclear magnetic resonance spectrum (400 MHz; $CDCl_3$; chemical shifts in ppm in ppm):

1.14 (s, 3H: $-C\underline{H}_3$ 16 or 17); 1.17 (s, 3H: $-C\underline{H}_3$ 16 or 17); 1.64 (s, 3H: $-C\underline{H}_3$ 19 or 18); 1.68 (s, 3H: $-C\underline{H}_3$ 19 or 18); 1.80 [mt, 1H: -(CH)-$\underline{H}$ 6]; 2.29 (mt, 2H: $-C\underline{H}_2$ 14); 2.37 (s, 3H: $-COC\underline{H}_3$); 2.57 [mt, 1H: -(CH)-$\underline{H}$ 6]; 3.40 and 3.77 (dd, J = 16, 1H each: $-C\underline{H}_2$ 10); 3.88 (broad s, 1H: -O$\underline{H}$ 2'); 4.03 (d, J = 7, 1H: -$\underline{H}$ 3); 4.18 and 4.29 (2d, J = 8, 1H each: $-C\underline{H}_2$ 20); 4.27 (mt 1H: -$\underline{H}$ 7); 4.78 (broad s, 1H: -$\underline{H}$ 2'); 4.93 (broad d, J = 9, 1H: -$\underline{H}$ 5); 5.68 (d, J = 7, 1H: -$\underline{H}$ 2); 5.78 (dd, J = 9 and 3, 1H: -$\underline{H}$ 3'); 6.10 (mt, 1H: -$\underline{H}$ 13); 7.20 (d, J = 9, 1H: -CON$\underline{H}$-); 7.30 to 7.45 (mt, 5H: $-C_6H_5$ 3'); 7.45 to 7.55 [mt, 5H: $-OCOC_6H_5$(-$\underline{H}$3 and -$\underline{H}$ 5) and $-NHCOC_6H_5$(-$\underline{H}$ 3, -$\underline{H}$ 4 and -$\underline{H}$ 5)]; 7.62 [t, J = 7.5, 1H: $-OCOC_6H_5$(-$\underline{H}$ 4)]; 7.75 (d, J = 7.5, 2H: $-NHCOC_5H_5$(-$\underline{H}$ 2 and -$\underline{H}$ 6)]; 8.12 [d, J = 7.5, 2H: $-OCOC_6H_5$(-$\underline{H}$ 2 and -$\underline{H}$ 6)].

EXAMPLE 3

The electrolytic reduction of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate (or docetaxel) is performed in an electrolysis cell possessing the following characteristics:

- the cell is a 100-cm^3 glass vessel divided into 2

compartments by a cation exchange membrane,

- the cathode is a layer of mercury whose useful surface area is 4 cm^2,
- the anode is a platinum grid,
- the reference electrode is a saturated calomel electrode.

20 cm^3 of a solution containing the following are introduced into the cathode compartment:

- docetaxel . . . . . 404.6 mg
- calcium chloride . . . . . q.s. 0.05 M
- methanol . . . . . q.s. 10 cm^3

10 cm^3 of a 0.5 M solution of hydrochloric acid in methanol are introduced into the anode compartment.

The solution is de-aerated by bubbling argon through it for 10 minutes, and the cathode potential is then set at -1.95 volts relative to the reference electrode. After 3 hours 49 minutes of electrolysis, that is to say the time needed for the passage of 197 coulombs, the electrolysis is stopped. 0.1 cm^3 of pure acetic acid and 0.5 cm^3 of saturated aqueous sodium hydrogen carbonate solution are added. After the solvent has been removed by concentration under reduced pressure, the residue is taken up with 20 cm^3 of ethyl acetate and 20 cm^3 of deionized water. After settling has taken place, the aqueous phase is extracted with twice 10 cm^3 of ethyl acetate. The organic phase is washed with 20 cm^3 of 0.2 M aqueous phosphate buffer

solution at a pH in the region of 7. After drying and concentration to dryness of the organic phase, 381.2 mg of a crude product are obtained, the constituents of which are separated by preparative thin-layer chromatography on silica gel. The crude product is taken up with the minimum amount of a dichloromethane/methanol (50:50 by volume) mixture and then injected onto 8 plates of silica gel (Kieselgel 60 F 254, Merck) 2 mm thick, eluting with a dichloromethane/acetonitrile/methanol (55:40:5 by volume) mixture. 116 mg of 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are thereby isolated in a 29.2 % yield, which product possesses the following characteristics:

- proton nuclear magnetic resonance spectrum (400 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz): 1.22 (s, 3H: $-CH_3$ 16 or 17); 1.26 (s, 3H: $-CH_3$ 16 or 17); 1.39 [s, 9H: $-C(CH_3)_3$]; 1.69 (s, 3H: $-CH_3$ 19); 1.79 (s, 3H: $-CH_3$ 18); 1.84 [ddd, J = 16, 9 and 2, 1H: -(CH)-H 6]; 2.33 (mt, 2H: $-CH_2$ 14]; 2.40 (s, 3H: $-COCH_3$); 2.65 [mt, 1H: -(CH)-H 6]; 3.42 (s, 1H: -OH 2'); 3.50 and 3.85 (dd, J = 16, 1H each: $-CH_2$ 10); 4.10 (d, J = 7, 1H: -H 3); 4.22 and 4.35 (2d, J = 8, 1H each: $-CH_2$ 20); 4.33 (mt, 1H: -H 7); 4.65 (dd, 1H: -H 2'); 5.00 (dd, J = 2 and 8, 1H: -H 5); 5.30 (broad d, J = 10, 1H: -H 3'); 5.45 (d, J = 10, 1H: -CONH-); 5.73

(d, J = 7, 1H: -H 2); 6.17 (broad t, J = 8, 1H: -H 13); 7.30 to 7.50 (m, 5H: $-C_6H_5$ 3'); 7.53 [t, J = 7.5, 2H: $-OCOC_6H_5$ (-H 3 and -H 5)]; 7.67 [t, J = 7.5 Hz, 1H: $-OCOC_6H_5$ (-H 4)]; 8.15 [d, J = 7.5, 2H: $-OCOC_6H_5$ (-H 2 and -H 6)].

EXAMPLE 4

The electrolytic reduction of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate is performed in an electrolysis cell possessing the following characteristics:

- the cell is a 120-cm^3 glass vessel divided into 2 compartments by a cation exchange membrane,
- the cathode is a layer of mercury whose useful surface area is 12 cm^2,
- the anode is a platinum grid,
- the reference electrode is a saturated calomel electrode.

20 cm^3 of a solution containing the following are introduced into the cathode compartment:

- 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate . . . . . 607.4 mg
- calcium chloride . . . . . q.s. 0.05 M
- methanol . . . . . q.s. 50 cm^3

10 cm^3 of a 0.5 M solution of hydrochloric

acid in methanol are introduced into the anode compartment.

The solution is de-aerated by bubbling argon through it for 10 minutes, and the cathode potential is then set to -2.0 volts relative to the reference electrode. After 2 hours 30 minutes of electrolysis, that is to say the time needed for the passage of 224 coulombs, the electrolysis is stopped. 10 cm^3 of a 0.1 M solution of sodium acetate in methanol are added. After the solvent has been removed by concentration under reduced pressure at a temperature below 35°C, the residue is taken up with 50 cm^3 of ethyl acetate and 50 cm^3 of deionized water. After settling has taken place, the aqueous phase is extracted with twice 25 cm^3 of ethyl acetate. The organic phase is washed with 25 cm^3 of 0.2 M aqueous phosphate buffer solution at a pH in the region of 7. After drying and concentration to dryness of the organic phase at a temperature below 35°C, 594.8 mg of a crude product are obtained, the constituents of which are separated by preparative thin-layer chromatography on silica gel. The crude product is taken up with the minimum amount of a dichloromethane/methanol (50:50 by volume) mixture and then injected onto 12 plates of silica gel (Kieselgel 60 F 254, Merck) 2 mm thick, eluting with a dichloromethane/acetonitrile/methanol (80:16:4 by volume) mixture. 229.4 mg of 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7α-dihydroxy-9-oxo-11-taxen-13α-yl

(2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate are thereby isolated in a 38.5 % yield, which product possesses the following characteristics:

- proton nuclear magnetic resonance spectrum (400 MHz; $CDCl_3$; chemical shift in ppm; coupling constants J in Hz): 1.10 (s, 3H: -C<u>H</u>$_3$ 16 or 17); 1.20 (s, 3H: -C<u>H</u>$_3$ 16 or 17); 1.36 [s, 9H: -C(C<u>H</u>$_3$)$_3$]; 1.62 (s, 3H: -C<u>H</u>$_3$ 19); 1.72 (s, 3H: -C<u>H</u>$_3$ 18); 1.73 (s, 1H: -O<u>H</u> 1); 2.15 to 2.45 (mt, 4H: -C<u>H</u>$_2$- 14 and -C<u>H</u>$_2$- 6); 2.49 (s, 3H: -COC<u>H</u>$_3$); 3.28 (broad s, 1H: -O<u>H</u> 2'); 3.43 (broad d, J = 16, 1H: -(CH)-<u>H</u> 10); 3.78 (ddd, J = 12.4 and 2.5, 1H: -<u>H</u> 7); 4.12 (d, J = 16, 1H: -(CH)-<u>H</u> 10); 4.20 (d, J = 7, 1H: -<u>H</u> 3); 4.38 (limiting ab, J = 11, 2H: -C<u>H</u>$_2$- 20); 4.58 (d, J = 12, 1H: -O<u>H</u> 7); 4.62 (broad s, 1H: -<u>H</u> 2'); 4.99 (dd, J = 9 and 5, 1H: -<u>H</u> 5); 5.28 (broad d, J = 10, 1H: -<u>H</u> 3'); 5.38 (d, J = 10, 1H: -CON<u>H</u>-); 5.76 (d, J = 7, 1H: -<u>H</u> 2); 6.17 (mt, 1H: -<u>H</u> 13); 7.30 to 7.45 (mt, 5H: -C_6H_5 3'); 7.52 [t, J = 7.5, 2H: -OCOC_6H_5 (-<u>H</u> 3 and <u>H</u> 5)]; 7.62 [t, J = 7.5, 1H: -OCOC_6H_5 (-<u>H</u> 4)]; 8.12 [d, J = 7.5, 2H: -OCOC_6H_5 (-<u>H</u> 2 and <u>H</u> 6)].

EXAMPLE 5

A first electrolytic reduction of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate is performed in an electrolysis cell possessing the following characteristics:

- the cell is a 100-cm^3 glass vessel divided into 2 compartments by a cation exchange membrane,
- the cathode is a layer of mercury whose useful surface area is 4 cm^2,
- the anode is a platinum grid,
- the reference electrode is a saturated calomel electrode.

10 cm^3 of a solution containing the following are introduced into the cathode compartment:

- 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate . . . . . 21.6 mg
- calcium chloride . . . . . q.s. 0.05 M
- methanol . . . . . q.s. 10 cm^3

10 cm^3 of a 0.1 M solution of hydrochloric acid in methanol are introduced into the anode compartment.

The solution is de-aerated by bubbling argon through it for 10 minutes, and the cathode potential is then set at -1.95 volts relative to the reference electrode at the beginning of the electrolysis and then at -2.0 volts after the passage of 10.5 coulombs. After 79 minutes of electrolysis, that is to say the time needed for the passage of 25.6 coulombs, the electrolysis is stopped.

A second electrolytic reduction of 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-

11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate is performed in the same one electrolysis cell.

20 cm^3 of a solution containing the following are introduced into the cathode compartment:

- 4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7α,10β-trihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate . . . . . 80.0 mg
- calcium chloride . . . . . q.s. 0.05 M
- methanol . . . . . q.s. 10 cm^3

10 cm^3 of a 0.1 M solution of hydrochloric acid in methanol are introduced into the anode compartment.

The solution is de-aerated by bubbling argon through it for 10 minutes, and the cathode potential is then set at -2.0 volts relative to the reference electrode. After 2 hours 4 minutes of electrolysis, that is to say the time needed for the passage of 66.5 coulombs, the electrolysis is stopped.

The electrolysis solutions are combined, and the medium is then buffered by adding a few cm^3 of a methanolic solution of acetic buffer. After the solvent has been removed by concentration under reduced pressure at a temperature below 35°C, the residue is taken up with 20 cm^3 of ethyl acetate and 20 cm^3 of deionized water. After settling has taken place, the aqueous phase is extracted with twice 10 cm^3 of ethyl

acetate. The organic phase is washed with 20 cm^3 of 0.2 M aqueous phosphate buffer solution at a pH in the region of 7. After drying and concentration to dryness of the organic phase at a temperature below 35°C, 95.7 mg of a crude product are obtained, the constituents of which are separated by preparative thin-layer chromatography on silica gel. The crude product is taken up with the minimum amount of a dichloromethane/methanol (50:50 by volume) mixture and then injected onto 1 plate of silica gel (Kieselgel 60 F 254, Merck) 2 mm thick, eluting with a dichloromethane/acetonitrile/methanol (80:16:4 by volume) mixture. 28.2 mg of 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7α-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate are thereby isolated in a 28 % yield, and 24.2 mg of 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate are thereby isolated in a 24 % yield, which products possess the following characteristics, respectively:

a). 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7α-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate:

- proton nuclear magnetic resonance spectrum (300 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz): 1.16 (s, 3H: $-CH_3$ 16 or 17); 1.21 (s, 3H: $-CH_3$ 16

or 17); 1.35 [s, 9H: -C(CH_3)$_3$]; 1.64 (s, 3H: -CH_3 19); 1.69 (s, 1H: -OH 1); 1.75 (s, 3H: -CH_3 18); 1.80 [mt, 1H: -(CH)-H 6]; 2.33 (mt, 2H: -CH_2 14]; 2.34 (s, 3H: -COCH_3); 2.61 [mt, 1H: -(CH)-H 6]; 3.40 (d, J = 5.5, 1H: -OH 2'); 3.44 and 3.80 (dd, J = 16, 1H each: -CH_2 10); 4.05 (d, J = 7, 1H: -H 3); 4.18 and 4.30 (2d, J = 8, 1H each: -CH_2 20); 4.27 (mt, 1H: -H 7); 4.62 (dd, J = 5.5 and 2, 1H: -H 2'); 4.94 (broad d, J = 9, 1H: -H 5); 5.25 (d, J = 10, 1H: -CONH-); 5.33 (broad d, J = 10, 1H: -H 3'); 5.70 (d, J = 7, 1H: -H 2); 6.13 (mt, 1H: -H 13); 7.13 (dd, J = 5 and 2, 1H: -H 4 of thiophene); 7.30 (dd, J = 3.5 and 2, 1H: -H 2 of thiophene); 7.36 (dd, J = 5 and 3.5, 1H: -H 5 of thiophene); 7.50 [t, J = 7.5, 2H: -OCOC_6H_5 (-H 3 and -H 5)]; 7.62 [t, J = 7.5, 1H: -OCOC_6H_5 (-H 4)]; 8.12 [d, J = 7.5, 2H: -OCOC_6H_5 (-H 2 and -H 6)].

b) 2α-benzoyloxy-4-acetoxy-5β,20-epoxy-1,7β-dihydroxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-(3-thienyl)-2-hydroxypropionate:

- proton nuclear magnetic resonance spectrum (300 MHz; $CDCl_3$; chemical shifts in ppm; coupling constants J in Hz): 1.12 (s, 3H: -CH_3 16 or 17); 1.20 (s, 3H: -CH_3 16 or 17); 1.35 [s, 9H: -C(CH_3)$_3$]; 1.62 (s, 3H: -CH_3 19); 1.68 (s, 1H: -OH 1); 1.72 (s, 3H: -CH_3 18); 2.20 to 2.50 (mt, 4H: -CH_2 14 and -CH_2 6); 2.44 (s, 3H: -COCH_3); 3.30 (broad s, 1H: -OH 2'); 3.42 and 4.10 (dd, J = 16.5, 1H each: -CH_2 10); 3.77 (ddd, J = 11.6 and 4, 1H: -H 7); 4.21 (d, J = 7, 1H: -H 3); 4.38 (broad s,

2H: $-C\underline{H}_2$ 20); 4.54 (d, J = 11, 1H: -O<u>H</u> 7); 4.62 (dd, J = 6 and 2.5, 1H: -<u>H</u> 2'); 4.89 (dd, J = 8.5 and 5.5, 1H: -<u>H</u> 5); 5.22 (d, J = 10, 1H: -CON<u>H</u>-); 5.34 (broad d, J = 10, 1H: -<u>H</u> 3'); 5.76 (d, J = 7, 1H: -<u>H</u> 2); 6.17 (mt, 1H: -<u>H</u> 13); 7.12 (broad d, J = 5, 1H: -<u>H</u> 4 of thiophene); 7.30 (broad d, J = 3.5, 1H; -<u>H</u> 2 of thiophene); 7.36 (dd, J = 5 and 3.5, 1H: -<u>H</u> 5 of thiophene); 7.52 [t, J = 7.5, 2H: $-OCOC_6\underline{H}_5$ (-<u>H</u> 3 and -<u>H</u> 5)]; 7.62 [t, J = 7.5, 1H: $-OCOC_6\underline{H}_5$ (-<u>H</u> 4)]; 8.14 [d, J = 7.5, 2H: $-OCOC_6\underline{H}_5$ (-<u>H</u> 2 and -<u>H</u> 6)].

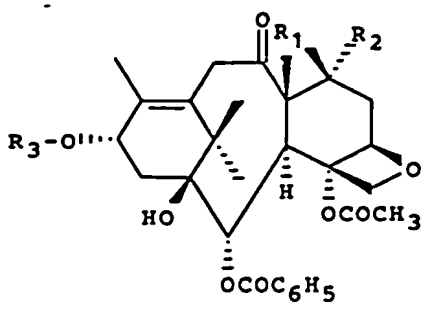
<u>EXAMPLE 6</u>

40 mg of 2α-benzoyloxy-1,7β-dihydroxy-5β,20-epoxy-9-oxo-11-taxen-13α-yl (2R,3S)-3-t-butoxycarbonylamino-3-phenyl-2-hydroxypropionate, obtained under the conditions of Example 1, are dissolved in 1 cm^3 of Emulphor EL 620 and 1 cm^3 of ethanol, and the solution is then diluted by adding 18 cm^3 of physiological saline.

The composition is administered by introduction in a perfusion of a physiological solution during 1 hour.

CLAIMS

1. Process for the preparation of taxane derivatives of general formula:

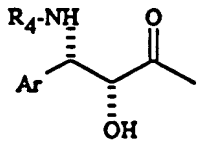


(I)

in which:

one of the symbols R_1 and R_2 represents a hydrogen atom and the other represents a hydroxyl radical,

- R_3 represents a hydrogen atom or a radical of general formula:

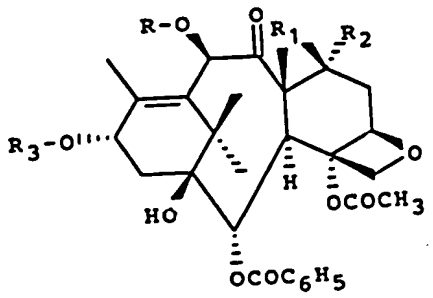


(II)

in which

Ar represents an aryl radical, and

R_4 represents a benzoyl radical or a radical R_5-O-CO in which R_5 represents an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclic radical, characterized in that the electrolytic reduction of a product of general formula:



(III)

in which R represents a hydrogen atom or an acetyl or alkoxyacetyl radical and R_1, R_2 and R_3 are defined as above, is performed in a solvent or mixture of solvents or an aqueous-organic mixture, in the presence of a carrier electrolyte.

2. Process according to claim 1, characterized in that the electrolyte consists of a magnesium, calcium, cerium^{III}, strontium or lithium salt or, where appropriate, when R represents an acetyl or alkoxyacetyl radical, of an ammonium salt which is soluble in the solvent or mixture of solvents or in the aqueous-organic mixture.

3. Process according to claim 2, characterized in that the salt is chosen from magnesium chloride, calcium chloride, cerium^{III} chloride, strontium chloride, lithium chloride and, where appropriate, ammonium chloride.

4. Process according to claim 2, characterized in that the solvents are chosen from aliphatic alcohols and the aqueous-organic mixture is an alcohol/water mixture.

5. Process according to claim 4, characterized in that the solvent is methanol.

6. Process according to one of claims 1 to 5, characterized in that the electrolysis is performed in an electrolyser containing a mercury cathode.

7. Process according to one of claims 1 to 5, characterized in that the electrolysis is preferably performed in a diaphragm electrolyser.

8. Process according to claim 7, characterized in that the diaphragm consists of a porous material or of a cation exchange membrane.

9. Process according to one of claims 1 to 8, characterized in that the electrolysis is performed at a controlled potential of between -1.65 and -2.1 volts relative to a calomel reference electrode, depending on the nature of the cation of the electrolyte;

10. Process according to one of claims 1 to 9 for the preparation of a product of general formula (I) in which in which, R_1 and R_2 being defined as in claim 1, R_3 represents a hydrogen atom or a radical of general formula (II) in which:

Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from fluorine or chlorine atoms and alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino,

dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals containing 1 to 4 carbon atoms and the aryl radicals are phenyl or α- or β-naphthyl radicals, or a 5-membered aromatic heterocyclic radical containing one or more identical or different atoms chosen from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents chosen from fluorine and chlorine atoms and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano, carboxyl and carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4

carbon atoms, and

R_4 represents a benzoyl radical or a radical R_5-O-CO- in which R_5 represents:

- an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from fluorine or chlorine atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino, morpholino and 1-piperazinyl (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms) radicals, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl, cyano and carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,
- a phenyl radical optionally substituted with one or more radicals chosen from alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl,

alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms,

- or a saturated 4- to 6-membered nitrogenous heterocyclic radical optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

11. Process according to one of claims 1 to 9 for the preparation of a product of general formula (I) in which, R_1 and R_2 being defined as in claim 1, R_3 represents a radical of general formula (II) in which Ar represents a phenyl radical optionally substituted with a fluorine or chlorine atom or with an alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino, alkoxycarbonylamino or trifluoromethyl radical or a 2- or 3-thienyl or 2- or 3-furyl radical, and R_4 represents a benzoyl radical or a radical R_5-O-CO- for which R_5 represents a t-butyl radical.

12. New taxane derivatives of general formula (I): R_1 and R_2 are defined as in claim 1, and R_3 represents a radical of general formula (II) in which Ar represents a heterocyclic radical defined as in one of claims 10 and 11 and R_4 represents a benzoyl radical

or a radical of general formula R_5-O-CO in which R_5 is defined as in one of claims 1, 10 and 11.

13. Pharmaceutical composition, characterized in that it contains a sufficient amount of at least one derivative according to claim 12, in the pure state or in combination with one or more pharmaceutically acceptable products.

IN THE MATTER OF an Australian
Application corresponding to
PCT Application PCT/FR93/01102

I, Philip Arnold KENDALL BSc ARCS MS PhD,
c/o Europa House, Marsham Way, Gerrards Cross, Buckinghamshire,
England, do solemnly and sincerely declare that I am conversant with the English and French languages and am a competent translator thereof, and that to the best of my knowledge and belief the following is a true and correct translation of the amended sheets of the PCT Application filed under No. PCT/FR93/01102.

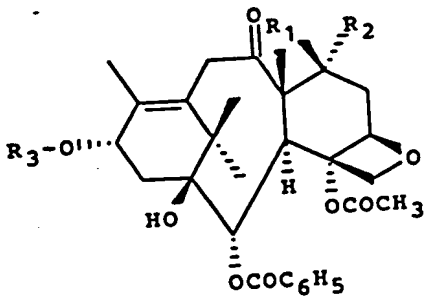
Date: 25 April 1995

P. A. Kendall

P. A. KENDALL
For and on behalf of RWS Translations Ltd.

CLAIMS

1. Process for the preparation of taxane derivatives of general formula:

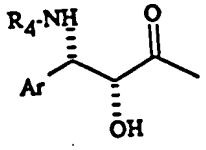


(I)

in which:

one of the symbols R_1 and R_2 represents a hydrogen atom and the other represents a hydroxyl radical,

- R_3 represents a hydrogen atom or a radical of general formula:

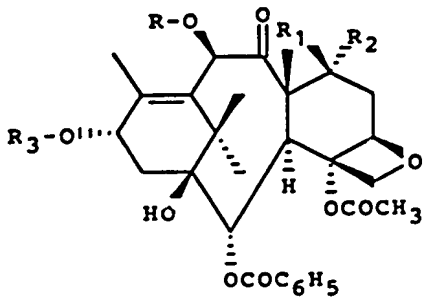


(II)

in which

Ar represents an aryl radical, and

R_4 represents a benzoyl radical or a radical R_5-O-CO in which R_5 represents an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclic radical, characterized in that the electrolytic reduction of a product of general formula:



(III)

in which R represents a hydrogen atom or an acetyl or alkoxyacetyl radical and R_1, R_2 and R_3 are defined as above, is performed in a solvent or mixture of solvents or an aqueous-organic mixture, in the presence of a carrier electrolyte.

2. Process according to claim 1, characterized in that the electrolyte consists of a magnesium, calcium, cerium^{III}, strontium or lithium salt or, where appropriate, when R represents an acetyl or alkoxyacetyl radical, of an ammonium salt which is soluble in the solvent or mixture of solvents or in the aqueous-organic mixture.

3. Process according to claim 2, characterized in that the salt is chosen from magnesium chloride, calcium chloride, cerium^{III} chloride, strontium chloride, lithium chloride and, where appropriate, ammonium chloride.

4. Process according to claim 2, characterized in that the solvents are chosen from aliphatic alcohols and the aqueous-organic mixture is an alcohol/water mixture.

5. Process according to claim 4, characterized in that the solvent is methanol.

6. Process according to one of claims 1 to 5, characterized in that the electrolysis is performed in an electrolyser containing a mercury cathode.

7. Process according to one of claims 1 to 5, characterized in that the electrolysis is preferably performed in a diaphragm electrolyser.

8. Process according to claim 7, characterized in that the diaphragm consists of a porous material or of a cation exchange membrane.

9. Process according to one of claims 1 to 8, characterized in that the electrolysis is performed at a controlled potential of between -1.65 and -2.1 volts relative to a calomel reference electrode, depending on the nature of the cation of the electrolyte;

10. Process according to one of claims 1 to 9 for the preparation of a product of general formula (I) in which in which, R_1 and R_2 being defined as in claim 1, R_3 represents a hydrogen atom or a radical of general formula (II) in which:

Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from fluorine or chlorine atoms and alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino,

dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals containing 1 to 4 carbon atoms and the aryl radicals are phenyl or α- or β-naphthyl radicals, or a 5-membered aromatic heterocyclic radical containing one or more identical or different atoms chosen from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents chosen from fluorine and chlorine atoms and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano, carboxyl and carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms and alkoxycarbonyl radicals in which the alkoxy portion contains 1 to 4

carbon atoms, and

R_4 represents a benzoyl radical or a radical R_5-O-CO- in which R_5 represents:

- an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from fluorine or chlorine atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino, morpholino and 1-piperazinyl (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms) radicals, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl, cyano and carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,
- a phenyl radical optionally substituted with one or more radicals chosen from alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl,

alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms,

- or a saturated 4- to 6-membered nitrogenous heterocyclic radical optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms,

on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

11. Process according to one of claims 1 to 9 for the preparation of a product of general formula (I) in which, R_1 and R_2 being defined as in claim 1, R_3 represents a radical of general formula (II) in which Ar represents a phenyl radical optionally substituted with a fluorine or chlorine atom or with an alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino, alkoxycarbonylamino or trifluoromethyl radical or a 2- or 3-thienyl or 2- or 3-furyl radical, and R_4 represents a benzoyl radical or a radical R_5-O-CO- for which R_5 represents a t-butyl radical.

12. New taxane derivatives of general formula (I): R_1 and R_2 are defined as in claim 1, and R_3 represents a radical of general formula (II) in which Ar represents a heterocyclic radical defined as in one of claims 10 and 11 and R_4 represents a benzoyl radical

or a radical of general formula R_5-O-CO in which R_5 is defined as in one of claims 1, 10 and 11.

13. Pharmaceutical composition, characterized in that it contains a sufficient amount of at least one derivative according to claim 12, in the pure state or in combination with one or more pharmaceutically acceptable products.

IN THE MATTER OF an Australian Application corresponding to PCT Application PCT/FR93/01102

I, Philip Arnold KENDALL BSc ARCS MS PhD, c/o Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, do solemnly and sincerely declare that I am conversant with the English and French languages and am a competent translator thereof, and that to the best of my knowledge and belief the following is a true and correct translation of the amended sheets of the PCT Application filed under No. PCT/FR93/01102.

Date: 25 April 1995

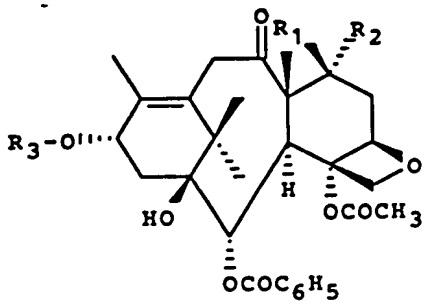
P. A. Kendall

P. A. KENDALL

For and on behalf of RWS Translations Ltd.

CLAIMS

1. Process for the preparation of taxane derivatives of general formula:

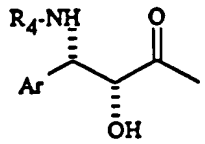


(I)

in which:

one of the symbols R_1 and R_2 represents a hydrogen atom and the other represents a hydroxyl radical,

- R_3 represents a hydrogen atom or a radical of general formula:

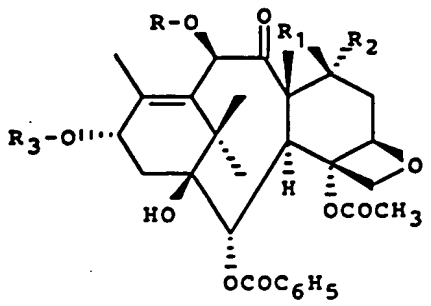


(II)

in which

Ar represents an aryl radical, and

R_4 represents a benzoyl radical or a radical R_5-O-CO in which R_5 represents an alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, phenyl or heterocyclic radical, characterized in that the electrolytic reduction of a product of general formula:



(III)

in which R represents a hydrogen atom or an acetyl or alkoxyacetyl radical and R_1, R_2 and R_3 are defined as above, is performed in a solvent or mixture of solvents or an aqueous-organic mixture, in the presence of a carrier electrolyte consisting of a magnesium, calcium, cerium^{III}, strontium or lithium salt or, where appropriate, when R represents an acetyl or alkoxyacetyl radical, of an ammonium salt which is soluble in the solvent or mixture of solvents or in the aqueous-organic mixture.

2. Process according to claim 1, characterized in that the salt is chosen from magnesium chloride, calcium chloride, cerium^{III} chloride, strontium chloride, lithium chloride and, where appropriate, ammonium chloride.

3. Process according to claim 1, characterized in that the solvents are chosen from aliphatic alcohols and the aqueous-organic mixture is an alcohol/water mixture.

4. Process according to claim 3, characterized in that the solvent is methanol.

5. Process according to one of claims 1 to 4, characterized in that the electrolysis is performed in an electrolyser containing a mercury cathode.

6. Process according to one of claims 1 to 4, characterized in that the electrolysis is preferably performed in a diaphragm electrolyser.

7. Process according to claim 6, characterized in that the diaphragm consists of a porous material or of a cation exchange membrane.

8. Process according to one of claims 1 to 7, characterized in that the electrolysis is performed at a controlled potential of between -1.65 and -2.1 volts relative to a calomel reference electrode, depending on the nature of the cation of the electrolyte.

9. Process according to one of claims 1 to 8 for the preparation of a product of general formula (I) in which in which, R_1 and R_2 being defined as in claim 1, R_3 represents a hydrogen atom or a radical of general formula (II) in which:

Ar represents a phenyl or α- or β-naphthyl radical optionally substituted with one or more atoms or radicals chosen from fluorine or chlorine atoms and alkyl, aryl, aralkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino,

aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals containing 1 to 4 carbon atoms and the aryl radicals are phenyl or α- or β-naphthyl radicals, or a 5-membered aromatic heterocyclic radical containing one or more identical or different atoms chosen from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents chosen from fluorine and chlorine atoms and alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 to 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 to 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxycarbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms, arylcarbonyl radicals in which the aryl portion contains 6 to 10 carbon atoms, cyano, carboxyl and carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion

contains 1 to 4 carbon atoms and alkoxycarbonyl radical in which the alkoxy portion contains 1 to 4 carbon atoms, and

R_4 represents a benzoyl radical or a radical R_5-O-CO- in which R_5 represents:

- an unbranched or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl radical containing 2 to 8 carbon atoms, an alkynyl radical containing 3 to 8 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, a cycloalkenyl radical containing 4 to 6 carbon atoms or a bicycloalkyl radical containing 7 to 10 carbon atoms, these radicals being optionally substituted with one or more substituents chosen from fluorine or chlorine atoms and hydroxyl radicals, alkoxy radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, piperidino, morpholino and 1-piperazinyl (optionally substituted at position 4 with an alkyl radical containing 1 to 4 carbon atoms or with a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms) radicals, cycloalkyl radicals containing 3 to 6 carbon atoms, cycloalkenyl radicals containing 4 to 6 carbon atoms, phenyl, cyano and carboxyl radicals and alkoxycarbonyl radicals in which the alkyl portion contains 1 to 4 carbon atoms,
- a phenyl radical optionally substituted with one or more radicals chosen from alkyl, aryl, aralkyl, alkoxy,

alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, acylamino, aroylamino, alkoxycarbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, carbamoyl, dialkylcarbamoyl, cyano and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms

- or a saturated 4- to 6-membered nitrogenous heterocyclic radical optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms, on the understanding that the cycloalkyl, cycloalkenyl or bicycloalkyl radicals may be optionally substituted with one or more alkyl radicals containing 1 to 4 carbon atoms.

10. Process according to one of claims 1 to 8 for the preparation of a product of general formula (I) in which, R_1 and R_2 being defined as in claim 1, R_3 represents a radical of general formula (II) in which Ar represents a phenyl radical optionally substituted with a fluorine or chlorine atom or with an alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino, alkoxycarbonylamino or trifluoromethyl radical or a 2- or 3-thienyl or 2- or 3-furyl radical, and R_4 represents a benzoyl radical or a radical R_5-O-CO- for which R_5 represents a t-butyl radical.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 93/01102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C25B3/04 C07D305/14 C07D409/12 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C25B C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 93, no. 9 , 5 May 1971 Washington, DC, US, pages 2325 - 2327 M.C. WANI, ET AL.: 'Plant tumour agents. VI. The isolation and structure of taxol, a novel antileukaemic and antitumour agent from Taxus brevifolia' see the whole document ---	1
A	EP,A,0 253 738 (RHONE-POULENC SANTE) 20 January 1988 cited in the application see page 2 - page 3 ---	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
31 January 1994	03. 02. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 93/01102

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COMPTES RENDUS DES SEANCES DE L'ACADEMIE DES SCIENCES. SERIE II:MECANIQUE, PHYSIQUE, CHIMIE, SCIENCES DE L'UNIVERS, SCIENCES DE LA TERRE, vol. 293, no. 7 , 29 October 1981 Montreuil, FR, pages 501 - 503 G. CHAUVIERE, ET AL.: 'Analyse structurale et étude biochimique de produits isolés de l'if: Taxus baccata L. (Taxacées)' -----	1

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RAPPORT DE RECHERCHE INTERNATIONALE

Dem· Internationale No
PCT/FR 93/01102

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 5 C25B3/04 C07D305/14 C07D409/12 A61K31/38

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 5 C25B C07D C07C

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 93, no. 9 , 5 Mai 1971 Washington, DC, US, pages 2325 - 2327 M.C. WANI, ET AL.: 'Plant tumour agents. VI. The isolation and structure of taxol, a novel antileukaemic and antitumour agent from Taxus brevifolia' voir le document en entier ---	1
A	EP,A,0 253 738 (RHONE-POULENC SANTE) 20 Janvier 1988 cité dans la demande voir page 2 - page 3 --- -/--	1

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

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Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
31 Janvier 1994	- 3. 02. 94

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	English, R

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter national Application No
PC1/FR 93/01102

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0253738	20-01-88	FR-A-	2601675	22-01-88
		AU-B-	591309	30-11-89
		AU-A-	7567787	21-01-88
		CA-A-	1278304	27-12-90
		JP-A-	63030479	09-02-88
		US-A-	4814470	21-03-89

RAPPORT DE RECHERCHE INTERNATIONALE

Dem · Internationale No
PCT/FR 93/01102

C(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	COMPTES RENDUS DES SEANCES DE L'ACADEMIE DES SCIENCES. SERIE II:MECANIQUE, PHYSIQUE, CHIMIE, SCIENCES DE L'UNIVERS, SCIENCES DE LA TERRE, vol. 293, no. 7 , 29 Octobre 1981 Montreuil, FR, pages 501 - 503 G. CHAUVIERE, ET AL.: 'Analyse structurale et étude biochimique de produits isolés de l'if: Taxus baccata L. (Taxacées)'	1

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RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs au... membres de familles de brevets

Dem... Internationale No
PCT/FR 93/01102

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
EP-A-0253738	20-01-88	FR-A-	2601675	22-01-88
		AU-B-	591309	30-11-89
		AU-A-	7567787	21-01-88
		CA-A-	1278304	27-12-90
		JP-A-	63030479	09-02-88
		US-A-	4814470	21-03-89